REMARKS

Supplemental to the Amendment submitted September 27, 2007, and the interview conducted October 3, 2007, applicant makes this submission.

A. Personal Interview:

Applicant thanks the Examiner and her supervisor for the courtesy extended the applicant's assignee's representatives during the interview conducted on October 3, 2007. Applicant appreciates the helpful comments provided during the interview.

During the interview, the Wilson et al. and Mahan references were discussed. As identified in the Examiner's Interview Summary,

> * Discussed composition claims and the concern of the variant of arginine levels. Applicants stated that the difference in amount is significant. As such, an Agreement that a Declaration would be submitted.
> * Discussed possible scope issue in regards to which animals are supported by the Specification.
> * Discussed replacing "comprising" [with] "consisting essentially of" in order to get around art of record.
> * Requested copy of NRC report discussed in Spec.

B. 35 U.S.C. § 103:

Claims 1 through 3 and 5 through 20 stand rejected as assertedly being obvious over Wilson et al. in view of Mahan. Applicant respectfully traverses the rejection for the reasons set forth in the Amendment under 37 C.F.R. § 1.114 filed September 27, 2007, the contents of which are incorporated herein by this reference.

C. Interview Discussion Points:

1. Declaration:

A declaration explaining the difference in arginine levels between the claimed composition and the Mahan reference was discussed. Submitted herewith is the Declaration of Dwain Guggenbiller, DVM.

2. Scope Issue With Respect To Which Animals Are Supported:

The question arose at the interview whether animals beyond pigs have written description

support in the as-filed patent specification. As discussed at the interview, the invention is admittedly primarily intended for pigs, but has broader application. As agreed at the interview, applicant supplements the discussion at the interview with the following disclosure from the as-filed patent application.

As set forth in the as-filed application,

> **[0002]** The invention relates, generally, to products and methods for increasing the productivity in farming by improving the fertility of healthy farming mammals, in particular pigs. More in particular, the invention relates to products and methods for improving the fertility of mammals by improvement of placentation in an animal, in particular by improvement of placentation which results from improved placental angiogenesis.
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> **[0004]** The term "fertility" as used in the present application and claims, is to be understood in a broad sense, *viz,* this term not only covers a decreased embryonic and fetal mortality, but also a decrease in perinatal and early neonatal losses of offspring, as well as a decrease in within-litter variation in development at birth. The improved fertility is reflected *e.g.* in an increased production of offspring for farming animals, such as pigs, or in an increased chance for viable offspring in case of animals, such as bovine or equine species or humans, which generally give birth to only a single individual per parturition.
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> **[0008]** Without wishing to be bound to theory, it is assumed that arginine improves angiogenesis and thus the vascularization of the placenta, by which the development of embryos and fetuses in the uterus is improved. As a result, a better placentation is observed in the animal by which a higher fertility and/or production of more viable offspring is obtained.
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> **[0012]** The invention is applicable to mammals in general, including humans. In the description below, the invention will mainly be illustrated with reference to pigs, but is not limited thereto.
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> **[0027]** The method, the animal feed and the premix according to the present invention, may be applied to various animals, in particular mammals. Preferred mammals are those that are agriculturally interesting, especially those selected from bovine species, equine species, porcine species, and ovine species. Also feeding to pet animals is envisaged.

(Specification, as-filed, underlining added).

Accordingly, applicant believes that "mammals" that undergo "placentation", "including humans" are described. "Preferred mammals are those that are agriculturally interesting,

especially those selected from bovine species, equine species, porcine species, and ovine species. Also feeding to pet animals is envisaged." Clearly, written description support exists for "animals".

Furthermore, applicant's theory of the invention, *i.e.*, "improve[d] angiogenesis and thus the vascularization of the placenta, by which the development of embryos and fetuses in the uterus is improved" should enable the invention to the broad category claimed.

Angiogenesis in the adult female is prominent in organs/tissues of the reproductive system, for instance, the uterus and placenta during pregnancy, and the ovaries, in which each specific phase of the hormonal cycle is accompanied by radical changes in vascular networks. Insufficient physiological angiogenesis can affect reproduction in all mammalian species at various levels:

- ovarian follicular development and thus the quality of the oocyte enclosed in the follicle and the developmental competence of this oocyte after fertilization. Insufficient follicular angiogenesis can thus lead to disruption of normal embryonic development and increased risk for embryo mortality.
- corpus luteum formation, and thus the regulation of normal ovarian cyclicality and, in case of pregnancy, the regulation of (early) pregnancy and maintenance of pregnancy.
- placentation, an essential process in early pregnancy and of the utmost importance for prenatal development and survival of the intra-uterine developing conceptus.

Insufficient physiological angiogenesis leads to ischemic conditions (shortage of both oxygen and nutrients) of the concerning organ/tissues. These ischemic conditions lead to the aforementioned negative effects on reproduction and reproductive success in humans and livestock species such as cattle, pigs, horses, sheep and other mammalian species in general.

Applicant investigated the possibility of increasing reproductive success in the pig (as a model for other livestock species and humans) by oral L-arginine supplementation of sows during a specific stage of pregnancy to improve placental angiogenesis, and thus reduce loss of fetuses during later stages of pregnancy due to placental insufficiency. Placental insufficiency is relatively common in the pig, but also a source of reproductive loss in humans and other mammalian species.

The results of these investigations confirmed the hypothesis that litter size at birth can be

increased (and therefore fetal mortality decreased) by oral L-arginine supplementation-mediated enhanced physiological angiogenesis during a critical window of placental development (Van der Lende and Ramaekers, 2002; Ramaekers et al., 2006; Hazeleger et al., 2007a,b).

Placental insufficiency due to suboptimal angiogenesis has been found to be a cause of poor prenatal development of the conceptus, and even reproductive losses, in various mammalian species other than the pig (Ahmed and Perkins, 2000; Regnault et al., 2003; Zygmunt et al., 2003; Mayhew et al., 2004; Redmer et al., 2004; Malamitsi-Puchner et al., 2005; Wallace et al., 2005; Wu et al., 2006).

The primary regulatory mechanism of placental physiological angiogenesis in adults is common for all mammalian species studied to date (*e.g.*, human, cattle, pigs, horses, sheep) (*see, e.g.*, Reynolds et al., 2005). Therefore, it is to be expected with a relatively high degree of certainty that oral L-arginine supplementation during a phase of physiological angiogenesis, will improve placental vascularization and thus prenatal development and survival in all these species. Likewise, oral L-arginine supplementation of adult females during well-chosen windows of physiological angiogenesis during ovarian follicle development (oocyte growth and development) and corpus luteum formation, should specifically improve angiogenesis with improved reproductive success as outcome. Again, in view of applicant's findings, this is to be expected, since for both physiological angiogenesis during follicular development and during corpus luteum formation, current knowledge indicates that the same primary regulatory mechanism of physiological angiogenesis operates as that in the placenta, again in all mammalian species studied to date (*see, e.g.*, Geva and Jaffe, 2000; Zimmermann et al., 2003, Tamanini and De Ambrogi, 2004; Berisha and Schams, 2005).

As previously set forth, although applicant believes the specification fully supports "animals", applicant is submitting new claims 22 and 23 directed to sows.

3. "Comprising" vs. "consisting essentially of":

The Examiner and her supervisor suggested that applicant amend the claims to recite "consisting essentially of" rather than "comprising" to further distinguish applicant's invention from that of the prior art. As discussed at the interview (and as set forth in the previous Amendment), applicant believes the invention is fully distinguished. However, in the spirit of

compromise, applicant is submitting new claims 21 and 23 which use the relatively more closed "consisting essentially of" transitional language.

4. National Research Council "Nutrient Requirements of Swine":

The Examiner requested that the applicant provide the National Research Council "Nutrient Requirements of Swine" report mentioned in paragraph **[0009]** of the Specification. (*See, e.g.*, page 16 of that report). Submitted herewith is a Supplemental Information Disclosure Statement submitting the report for the Office's consideration.

If questions remain after consideration of the foregoing, the Office is kindly requested to contact applicant's attorney at the address or telephone number given herein.

Respectfully submitted,

Allen C. Turner
Registration No. 33,041
Attorney for Applicant
TRASKBRITT, P.C.
P.O. Box 2550
Salt Lake City, Utah 84110-2550
Telephone: 801-532-1922

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Enclosures: Supplemental Information Disclosure Statement
Declaration of Dr. Dwain J. Guggenbiller